510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number:

k120994

B. Purpose for Submission:

To obtain a substantial equivalent determination for a premarket notification for the BD BACTEC Plus PRIME Aerobic/F blood culture medium.

C. Measurand:

Aerobic bacteria and yeast

D. Type of Test:

Liquid culture medium for recovery of microorganisms (bacteria and yeast) from blood using fluorescent instruments to detect increased CO_2

E. Applicant:

Becton Dickinson and Company

F. Proprietary and Established Names:

BD BACTEC Plus PRIME Aerobic /F

G. Regulatory Information:

1. Regulation section:

   21 CFR 866.2560

2. Classification:

   Class I

3. Product code:

   MDB

4. Panel:

   83 Microbiology

H. Intended Use:

1. Intended use:

   The BD BACTEC Plus PRIME Aerobic/F medium is used in a qualitative procedure for the aerobic culture and recovery of microorganisms (bacteria and yeast) from blood. The principal use of this medium is with the BD BACTEC fluorescent series instruments.

2. Indications for use:

   The BD BACTEC Plus Aerobic/F medium is used in a qualitative procedure for the aerobic culture and recovery of microorganisms (bacteria and yeast) from blood. The principal use of this medium is with the BD BACTEC fluorescent series instruments.

3. Special conditions for use statement(s:

   Prescription use

4. Special instrument requirements:

   BD BACTEC fluorescent series instrument

I. Device Description:

The sample to be tested is inoculated into one or more vials which are inserted into the BACTEC fluorescent series instrument for incubation and periodic reading. Each vial contains a chemical sensor which can detect increases in CO_2 produced by the growth of microorganisms. The sensor is monitored by the instrument every ten minutes for an increase in its fluorescence, which is proportional to the amount of CO_2 present. A positive reading indicates the presumptive presence of viable microorganisms in the vial. Detection is limited to microorganisms that will grow in a particular type of medium.

Resins have been described for the treatment of blood specimens both prior to and after their inoculation into culture media. Resins have been incorporated into BACTEC culture media to enhance recovery of organisms without a need for special processing.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   BD BACTEC Plus Aerobic /F medium

2. Predicate k number(s):

   k083572

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	Qualitative procedure for the aerobic culture and recovery of microorganisms (bacteria and yeast) from blood, with the BD BACTEC fluorescent series instrument	Same
Specimen type	Human blood	Same
Maximum blood to broth ratio	1:4	Same
Instrumentation	BD BACTEC fluorescent series	Same
Detection Technology	Continuous monitoring; incorporate chemical sensor for detection of CO_2 increases produced by the growth of aerobic bacteria and yeast	Same
Incubation	35ºC (± 1.5ºC) up to 120 hrs	Same
Vial	Glass	Same

Differences		
Item	Device	Predicate
Resin blend formulation	Two hydrophobic absorbing resins	One hydrophobic absorbing resins
Resin blend weight per bottle	Decreased	--
Percent oxygen in head space	changed	--
Sodium polyanetholsulfonate (SPS) concentration	0.085%	0.05%

K. Standard/Guidance Document Referenced (if applicable):

Not applicable

L. Test Principle:

If microorganisms are present in the test sample inoculated into the BACTEC vial, CO_2 will be produced when the organisms metabolize the substrates present in the vial. Increases in the fluorescence of the vial sensor caused by the higher amount of CO_2 are monitored by the BACTEC fluorescent series instrument. Analysis of the rate and amount of CO_2 increase enables the BACTEC fluorescent series instrument to determine if the vial is positive, i.e., that the test sample contains viable organisms.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

The reproducibility study was evaluated by time to detection and recovery, in the Instrument Time to Detection and Recovery studies across three lots. Results exhibited no statistically significant difference.

b. Linearity/assay reportable range:

Not applicable

c. Traceability, Stability, Expected values (controls, calibrators, or methods):

The range of time-to-detection in hours was ≤ 72 hours for each of the organisms listed below. The QC study was performed on three lots and the QC specifications were met.

Aerobic Medium Organisms

Neisseria meningitidis ATCC 13090	*Candida glabrata* ATCC 66032
Haemophilus influenzae ATCC 19418	*Staphylococcus aureus* ATCC 25923
*Streptococcus pneumoniae** ATCC 6305	*Escherichia coli* ATCC 25922
Streptococcus pyogenes ATCC 19615	*Alcaligenes faecalis* ATCC 8750
Pseudomonas aeruginosa ATCC 27853	

*CLSI recommended strain

d. Detection limit:

Microbial Detection Limit study

The test includes 15 strains tested at two blood volumes, each with two inoculum levels over three lots for a total of 180 paired sets:

15 strains x 2 blood volumes x 2 inoculum levels x 3 lots = 180

Microbial Detection Limit Comparison summary

Condition	Number of Bottles
Growth and detection in both the new and predicate device	89
Growth and detection in the predicate device only	30
Growth and detection in the new device only	23
No growth and detection in either the new or predicate devices	38
McNemar p-value	0.3363

Of the 30 cultures that were positive only in the predicate device, 23 of those that were negative cultures in the new device had low inoculum (0 to 1 CFU per bottle) levels. The remaining seven failures were at the 1 to 10 CFU per bottle inoculum level. The organisms were *Cryptococcus neoformans, Micrococcus luteus, Staphylococcus epidermidis* (3 and 10 mL of blood), *Streptococcus pneumoniae* (two replicates at 3 mL of blood) and *Streptococcus sanguinis*.

Of the 23 cultures that were positive only in the new device, 19 had low inoculum (0 to 1 CFU per bottle) levels. The remaining four failures were at the 1 to 10 CFU per bottle inoculum level. The four that failed to detect in the 1 to 10 CFU range included *Candida glabrata, Micrococcus luteus, Staphylococcus epidermidis and Streptococcus pneumoniae*.

Thirty-eight species failed to detect in both the new and predicate devices. Thirty-three of the failures were at the lowest dilution (0 to 1 CFU per bottle) and 5 were at the 1 to 10 CFU per bottle dilution: *Escherichia coli, Haemophilus parainfluenzae,* and *Streptococcus pneumoniae*.

The claim for the new BD BACTEC Plus PRIME Aerobic /F bottle was 10-100 CFU/bottle. This data is therefore acceptable for the claimed microbial detection level.

e. Analytical specificity:

Not applicable

f. Assay cut-off:

Not applicable

2. Comparison studies:

Performance of the BD BACTEC Plus PRIME Aerobic/F medium was evaluated on three lots during internal analytical studies to demonstrate comparable performance to the predicate device – the BD BACTEC Plus Aerobic/F medium. All studies utilized the BD BACTEC FX fluorescent-series instrument operating on the released software (4.10a).

Percent Recovery (Sensitivity) study

A total of 246 paired sets at 10 to 100 CFU per bottle were evaluated in the Percent Recovery comparison. The study included six replicate paired sets per organism and there were a total of 41 organisms. The six replicate paired sets are comprised of three lots with two blood volumes per lot for both the new and predicate devices. There were 244 (99.2%) positive in both the new and predicate devices.

Condition	Number of Bottles
Detected in both the new and predicate devices	244 per device
Detected in the predicate device only	2
Detected in the new device only	0
Not detected in either device	0

The two recovery failures observed were with *Kingella kingae.* Subsequent testing of five isolates of *K. kingae*, including the false negative isolate noted above, under the same test conditions and over three lots all demonstrated growth and recovery as expected.

Instrument Time to Detection

The Instrument Time to Detection (TTD) study included blood volumes, and organisms. The TTD study included data from both the Percent Recovery and Microbial Detection Limit studies. Each organism was inoculated at appropriate inoculum levels, across two blood volumes (3 mL and 10 mL) over three lots of media. The Microbial Detection Limit study was conducted at the lower inoculum levels (replicates at 0 – 1 CFU, 1 – 10 CFU per bottle); the Percent Recovery study at 10 – 100 CFU per bottle.

The following organisms had a mean TTD difference that was more rapid in the predicate device: *Abiotrophia defectiva* (2.39 h), *Acinetobacter lwoffii* (0.97), *Cardiobacterium hominis* (3.11 h), *Haemophilus influenzae* (3.70 h), *Streptococcus sanguinis* (8.12 h), *Candida albicans* (0.75 h), *Enterococcus faecalis* (0.62 h), *Granulicatella spp.* (1 h), *Kingella kingae* (4.38 h), *Micrococcus luteus* (1.06 h), *Pediococcus acidilactici* (1.08 h) and *Streptococcus pneumoniae* (0.81 h). *Leuconostoc spp.* exhibited a mean TTD difference increase of 10.00 h compared to the predicate device (mean TTD of 69.21 h), an increase of 14.45% in the new device.

False Positive Rate Study

False positivity was assessed with bottles inoculated with freshly drawn human blood (i.e. 2, 4, 6, 8 and 10 mL). No organisms were added to the bottle. There were 120 bottles per device across three lots. No positive results were observed.

False Negative Rate Study

The data for this study was generated from the Instrument Time to Detection, Percent Recovery (Sensitivity), and Microbial Detection Limit studies. Bottles that are instrument negative at 120 hours and found to be positive when subcultured are classified as false negative bottles.

A total of 93 paired sets were evaluated to determine the false negatives, with the following results:

Detected in predicate device only	32
Detected in new device only	23
Detected in neither devices (Negatives)	38 paired sets

There were a total of 12 false negative bottles with instrument negative, subculture positive. There were eight false negative results with the BACTEC Plus PRIME Aerobic/F: *Micrococcus luteus*, *Cryptococcus neoformans* and six replicates of *Haemophilus parainfluenzae* biotype I. There were four false negative results with the predicate device: two replicates of *Haemophilus parainfluenzae* biotype I, *Cryptococcus neoformans* and *Candida glabrata*.

There were two false negative bottles with both instrument and subculture negative: two replicates of *Kingella kingae* with 3 mL of blood (plate count 31 CFU) in the new BACTEC Plus PRIME Aerobic/F media. Subsequent testing of five additional isolates of *K. kingae*, including the false negative isolate noted above, at inoculum 50-100 CFU and across three lots all demonstrated recovery of *Kingella kingae.*

There was no statistically significant difference in the false negative rate between the new BACTEC Plus PRIME Aerobic/F media and the predicate device.

Antimicrobial Neutralization Capability

The ability of the medium to recover organisms in the presence of eleven antimicrobials at minimum inhibitory concentration (MIC) levels was evaluated. Each antimicrobial was tested with three organisms that would be appropriately treated with the drug and each organism was susceptible to the drug at the concentration inoculated into the bottle. The bottles were then assessed for recovery. There were a total of 99 paired sets for this study.

The antimicrobial classes evaluated in this study were: Aminoglycosides, Carbapenems, Glycopeptides, 3rd gen. Cephalosporins, Fluoroquinolones, Tetracyclines, 4th gen. Cephalosporins, Monobactams, Triazoles, Glycylcycline, +Penicillins / β-lactamase inhibitors

MIC Level Drug-Bug Recovery Pair Wise Comparison

		Predicate Device		
		Detected	Not Detected	Total
New Device	Detected	94	1	95
	Not Detected	2	2	4
	Total	96	3	99

MIC Level Drug-Bug Recovery Comparison

		Predicate		New Device	
Drug	Class	Detected	Not Detected	Detected	Not Detected
Aztreonam	Monobactam	6	3	5	4
Ciprofloxacin	Floroquinolones	9	0	9	0
Cefotaxime	3rd gen. Cephalosporin	9	0	9	0
Fluconazole	Triazole	9	0	9	0
Cefepime	4th gen. Cephalosporin	9	0	9	0
Gentamicin	Aminoglycoside	9	0	9	0
Meropenem	Carbapenem	9	0	9	0
Tetracyclin	Tetracyclin	9	0	9	0
Tigecycline	Glycylcycline	9	0	9	0
Piperacillin-Tazobactam	Penicillin – β-lactamase inhibitor	9	0	9	0
Vancomycin	Glycopetide	9	0	9	0
	Total	**96**	**3**	**95**	**4**

The data demonstrated that in the presence of Aztreonam at MIC level, the ability of the new medium to recover organisms was 55.6% (5/9), and 66.7% (6/9) for the predicate medium. Monobactams (Aztreonam) and Carbapenems were not included in the predicate device when cleared. The performance of the carbapenem was acceptable.

A subset of five commonly-used antimicrobials representative of their classes was further evaluated at peak serum levels, concentrations at an average of 20x the MIC of the test organisms. Each antimicrobial was tested with organisms that would be appropriately treated with the drug and each organism was susceptible to the drug at the concentration inoculated into the bottle. There were 150 paired sets of which 66 pair sets were not detected in both the predicate and the new devices:

Peak Serum Level Drug-Bug Challenge Summary

		Predicate		
		Detected	Not Detected	Total
New Device	Detected	32	44	76
	Not Detected	8	66	74
	Total	40	110	150

Peak Serum Level Drug-Bug Challenge Results by Drug

	Predicate		New Device	
Drug	Detected	Not Detected	Detected	Not Detected
Amoxicillin – Clavulanate	3	27	12	18
Cefotaxime	5	25	10	20
Cefepime	12	18	20	10
Gentamicin	17	13	21	9
Meropenem	3	27	13	17
Total	40	110	76	74

The overall recovery rate for the BD BACTEC Plus PRIME Aerobic/F medium was 51% vs. 27% for the BD BACTEC Plus Aerobic/F medium. The target organism concentrations for these studies were 10- 100 CFU/bottle, and 7 mL of blood were used.

a. *Method comparison with predicate device:*

   Performance of the new BD BACTEC Plus PRIME Aerobic /F Plastic was compare to that of the BACTEC Plus Aerobic/F medium.

b. Matrix comparison:

BD BACTEC Plus culture media, human blood volume, common bloodstream pathogens

3. Clinical studies:

Not Applicable, analytical seeded studies for comparison between the new BD BACTEC Plus PRIME Aerobic /F and the BACTEC Plus Aerobic/F medium.

a. Clinical Sensitivity:

Not Applicable

*b. Clinical specificity**:***

Not Applicable

c. Other clinical supportive data (when a. and b. are not applicable):

Not Applicable

4. Clinical cut-off**:**

Not Applicable

5. Expected values/Reference range:

Seeded studies performed by BD have shown equivalent performance of the BD BACTEC Plus PRIME Aerobic /F medium compared to the BD BACTEC Plus Aerobic/F medium.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.